Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of the Claims:

1. (currently amended): A method for delivery and retention of an active agent in one or more targeted lymph nodes, comprising:

   a) injecting into a mammal a first composition comprising ligand conjugated to a colloid; and

   b) injecting into said mammal a second composition comprising anti-ligand, wherein said anti-ligand binds to said ligand prior to entering the lymph node.

2. (original) The method of claim 1, wherein the colloid comprises a liposome.

3. (original) The method of claim 2, wherein the liposome comprises phospholipid.

4. (original) The method of claim 2, wherein the liposome comprises cholesterol.

5. (original) The method of claim 3, wherein the phospholipid comprises DPPC or DSPC.

6. (original) The method of claim 1, wherein the ligand comprises biotin.

7. (original) The method of claim 1, wherein the anti-ligand comprises avidin.

8. (original) The method of claim 1, wherein the colloid is associated with an active agent.

9. (original) The method of claim 8, wherein the active agent is chosen from the group consisting of diagnostic agents, therapeutic agents, photoactivated dyes, cytotoxic agents, biological response modifiers, hormone suppressants, prodrugs, dyes for visual detection,

radiosensitizers, radioprotectors, DNA, RNA, antigens, radioisotopes and neutron capture isotopes.

10. (original) The method of claim 9, wherein the active agent is chosen from the group consisting of radioisotopes and dyes.

11. (original) The method of claim 9, wherein the active agent is chosen from the group consisting of diagnostic agents and dyes for visual detection.

12. (original) The method of claim 9, wherein the active agent is chosen from the group consisting of photoactivated dyes, cytotoxic agents, biological response modifiers, hormone suppressants, prodrugs, radiosensitizers, radioprotectors, DNA, RNA, and neutron capture agents.

13. (original) The method of claim 1, wherein the anti-ligand comprises an active agent.

14. (original) The method of claim 1, wherein the ligand comprises biotin and the anti-ligand comprises avidin.

15. (currently amended) A method for detecting one or more sentinel lymph nodes comprising:

a) injecting in the vicinity of a tumor in a mammal a first composition comprising ligand conjugated to a colloid; and

b) injecting into said mammal a second composition comprising anti-ligand, wherein said anti-ligand binds to said ligand <u>prior to entering the lymph node</u>.

16. (original) The method of claim 15, wherein the colloid comprises an active agent.

17. (original) The method of claim 16, wherein the active agent is chosen from the group consisting of radioisotopes and dyes.

18. (original) The method of claim 15, wherein the anti-ligand comprises a detection agent.

19. (original) The method of claim 18, wherein the detection agent comprises a radioisotope or dye.

Claims 20-28 (cancelled).

29. (previously presented): The method of claim 9, wherein the active agent comprises a radioisotope and a dye.

30. (previously presented): The method of claim 16, wherein the active agent comprises a radioisotope and a dye.

31. (new): The method of claim 1, wherein the colloid comprises a size range of 1 to 5,000 nm.

32. (new): The method of claim 31, wherein the colloid comprises a size range of 5 to 500 nm.

33. (new): The method of claim 32, wherein the colloid comprises a size range of 50 to 300 nm.

34. (new): The method of claim 1, wherein the first and second compositions are administered by subcutaneous, subdermal, submucosal, intraperitoneal, intrapleural, intraarticular, intramucosal, intramuscular, intradermal, intratumoral, interstitial, intraorgan, intracavitary, intralymphatic, intralesion, or intraosseal injection.

35. (new): The method of claim 15, wherein the colloid comprises a size range of 1 to 5,000 nm.

36. (new): The method of claim 35, wherein the colloid comprises a size range of 5 to 500 nm.

37. (new): The method of claim 36, wherein the colloid comprises a size range of 50 to 300 nm.

38. (new): The method of claim 15, wherein the first and second compositions are administered by subcutaneous, subdermal, submucosal, intraperitoneal, intrapleural, intraarticular, intramucosal, intramuscular, intradermal, intratumoral, interstitial, intraorgan, intracavitary, intralymphatic, intralesion, or intraosseal injection.

A Response to the Office Action:

A. A Status of the Specification

The specification has been amended to correct a minor typographical error. Applicants' claim to priority which was added by amendment on January 11, 2002 inadvertently recited, in part, "U.S. Provisional Application No.: 06/143,742" instead of "U.S. Provisional Application No.: 60/143,742" (emphasis added). At the suggestion of the Action, the specification has been amended to correct this typographical error. No new matter has been added by this amendment. Applicants request that the objection to the specification be withdrawn.

B. A Status of the Claims

Claims 1-30 were pending when the Office Action dated February 17, 2004 was mailed to Applicants. Claims 1, 15, 20, and 25 have been amended and new claims 31-38 have been added. Support for the amendments and the new claims can be found throughout the specification and claims as originally filed. *See, e.g.*, the specification, page 12, line 32, to page 13, line 10; page 13, lines 17-19; and page 14, lines 14-17.

Claims 20-28 have been cancelled without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of these claims in a future continuing application. Claims 1-19 and 29-38, therefore, are currently pending.

C. A Response to the Office Action

1. The Enablement Rejection Is Improper

Claims 1-30 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Action contends that the specification does not enable the full scope of the present claims. In summary, the Action takes the position that the present claims "embrace the use of an enormous number of colloid particles, regardless of their sizes ... ." The Action, page 4. The

Action cites to Oussoren *et al.* for the proposition that larger liposomes have problems entering lymph nodes. *Id.* From this, the Action concludes that "one skilled in the art would not have been able to reasonably extrapolates, from the teachings and/or working examples provided by the specification to the entire breadth of the claimed invention." The Action admits, however, that claims directed towards a colloidal particle "with a size range of less than 500 nm" are enabled by the specification. *Id.* at page 6. The Action also contends that the present claims are only enabled where the ligand/anti-ligand formation occurs "prior to their entry into the targeted lymph nodes through the lymphatic system." The Action, page 6.

Applicants traverse. Claims 1-30 satisfy all of the requirements of 35 U.S.C. § 112, first paragraph.

2. The Standard for Enablement

It is well-settled that "the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." *Manual of Patent Examining Procedure* (MPEP) § 2164.04 (inc. rev. 1, 2003). The standard for enablement has been stated by the Federal Circuit as:

> The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation.

United States v. Telectronics, Inc., 857 F.2d 778, 785 (Fed. Cir. 1988); *see also* MPEP § 2164.01. Enablement must bear only a ***reasonable*** relationship to the scope of the claims. *See In re Fisher*, 166 U.S.P.Q. 18, 24 (CCPA 1970). Moreover, the Federal Circuit has held that "[t]he enablement requirement is met if the description enables ***any*** mode of making and using the invention." *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1361 (Fed. Cir. 1998) (emphasis added) (quoting *Engel Indus. Inc. v. Lockformer Co.*, 946 F.2d 1528, 1533 (Fed. Cir. 1991)) (emphasis added). The MPEP confirms this by stating that "when a compound or

composition claim is not limited by a recited use, ***any enabled use*** that would reasonably correlate with the entire scope of that claim ***is sufficient*** to preclude a rejection for nonenablement based on that use." MPEP § 2164.01(c) (emphasis added). All that is required for enablement is objective enablement, not any particular level of efficacy. *In re Marzocchi*, 169 UPSQ 370 (CCPA 1971).

3. The Present Claims Are Enabled By the Specification

i. The specification teaches how to make the claimed invention.

A person of skill in the art could make the presently claimed invention from the disclosure in the specification alone or in combination with information known in the art without undue experimentation. By way of example only, Examples 7-8 and 10 of the present specification disclose at least methods of preparing: (1) ligand-colloid conjugates; (2) biotin-colloid conjugates encapsulating blue dye; and (3) anti-ligand-active agent compositions, respectively. Specification, pages 30-33. The Examples provide several types of non-limiting examples of ligands, colloids, and anti-ligands that can be used with the present invention. *Id.* Also disclosed in the Examples are suggestions where such ingredients can be obtained. *Id.* The Action, in fact, does not appear to contend that the specification fails to teach a person of skill in the art how to make the present invention. The specification, therefore, teaches a person how to make the present invention.

ii. The specification teaches how to use the claimed invention.

The specification also teaches a person of reasonable skill in the art how to use the present invention. The specification provides data showing that the methods and compositions of the present invention can be used, for example, "for delivery and retention of an active agent in one or more targeted lymph nodes." *See, e.g.*, Examples 13-19 of the specification. Example

13, *e.g.*, provides data showing an increased retention of liposomes in lymph nodes by using labeled biotin-liposomes along with avidin. *See id.* at page 38, lines 23-26. Table 1 of the specification provides surprising and unexpected results showing an increased retention of liposomes in a targeted lymph node when compared to a control (without avidin). *Id.* at page 39. Based on this evidence alone, the presently claimed invention is fully enabled by the specification. *See Johns Hopkins Univ.*, 152 F.3d at 1361 (noting that "[t]he enablement requirement is met if the description enables any mode of making and using the invention.").

Further, the Action's suggestion that the full scope of the present claims are not enabled by the specification is without basis. The Action's contention that the present claims "embrace the use of an enormous number of colloid particles, regardless of their sizes" ignores the claim language of at least pending claims 1 and 15. Present claim 1, for example, is directed towards "[a] method for ***delivery and retention*** of an active agent ***in one or more targeted lymph nodes***." Claim 1 (emphasis added). Claim 15 is directed towards "[a] method for ***detecting one or more sentinel lymph*** nodes." Claim 15 (emphasis added). The emphasized language is evidence that the colloidal particle size must be of a sufficient size to be delivered and retained in the targeted lymph node or to detect a sentinel lymph node. The present claims include colloidal particle sizes that can be delivered and retained in a targeted lymph node. A person of reasonable skill in the art would be able to determine the size of such a colloidal particle by running assays such as the assays used in at least Example 13 of the present specification—this can be done without undue experimentation. *See In re Fisher*, 166 U.S.P.Q. at 24 (noting that enablement must bear only a ***reasonable*** relationship to the scope of the claims); *see also* MPEP § 2164.01 ("The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.").

The Action's position that the present claims are only enabled where the ligand/anti-ligand aggregation occurs "prior to their entry into the targeted lymph nodes" is similarly without merit. At the suggestion of the Action, however, and to obtain commercially relevant claims at this time, claims 1 and 15 have been amended to recite "wherein said anti-ligand binds to said ligand prior to entering the lymph node." The present enablement rejection on this ground is therefore rendered moot.

The rejection of the present claims under 35 U.S.C. § 112, first paragraph, for lacking enablement should be withdrawn in view of at least the above statements.

4. The Anticipation Rejection Is Improper

The Action rejects claims 20-27 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,527,528 to Allen *et al.* ("Allen *et al.*"). The Action contends that this reference discloses a kit having an anti-ligand, a ligand conjugated to a liposome which entrapped a therapeutic agent and/or a radioisotope. From this, the Action concludes that claims 20-27 are anticipated by Allen *et al.*

Applicants traverse. Claims 20-27 are not anticipated by Allen *et al.*

Allen *et al.* fails to teach each and every aspect of claims 20-27. However, to obtain commercially relevant subject matter at this time, claims 20-27 have been canceled without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of these claims in a future continuing application.

The anticipation rejection of claims 20-27 is therefore rendered moot. Applicants request that this rejection be withdrawn.

5. The Obviousness Rejection of Claims 25 and 28 Is Improper

Claims 25 and 28 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Allen *et al.* in view of U.S. Patent No. 5,143,713 to Phillips *et al.* (Phillips *et al.*) and U.S. Patent No. 5,482,698 to Griffiths (Griffiths). These claims are not obvious over the cited references. However, to obtain commercially relevant subject matter at this time, claims 25 and 28 have been cancelled without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of these claims in a future continuing application.

The obviousness rejection of claims 25 and 28 is therefore rendered moot. Applicants request that this rejection be withdrawn.

6. The Obviousness Rejection of Claims 1-19 and 29-30 Is Improper

i. A summary of the rejection and the standard for establishing a prima facie case of obviousness.

The Action also rejects claims 1-19 and 29-30 under 35 U.S.C. § 103(a) as being unpatentable over the teachings of Allen *et al.* in view of either Griffiths or U.S. Patent No. 5,420,105 to Gustavson *et al.* and in further view of Oussoren. The Action contends that Allen *et al.* discloses a method of delivering a first composition comprising a ligand conjugated to a tumor specific antibody and delivering a second composition comprising an anti-ligand/therapeutic agent/diagnostic agent containing liposomal carriers. The Action, page 10. The Action, however, admits that Allen *et al.* fails to teach that the liposomal particle can also be used to enhance the delivery of the first composition comprising a tumor specific antibody conjugated to a ligand such as biotin. The Action, page 11. The Action also admits that Allen *et al.* fails to disclose that a dye can be used to enhance the visualization of the delivered agents in a treated subject.

To supplement the deficient teachings of this reference, the Action cites to Gustavson *et al.* and Griffiths and contends that these secondary references disclose the use of a colloidal based system is effective to increase the targeting of both a ligand conjugate or a subsequent anti-ligand conjugate at an intended target site such as a tumor site. The Action cites to Oussoren and contends that it discloses that colloidal particles up to about .4 um in diameter are transported from an injection site into the lymphatic capillaries and localized in regional lymph nodes. From this, the Action concludes that it would have been obvious for one of ordinary skill in the art to employ a colloidal based delivery carrier to enhance the delivery and binding of ligand/anti-ligand at a target tumor site to which the first delivered ligand is bound. The Action, page 11.

Applicants traverse the obviousness rejection. The pending claims are not rendered obvious over the cited references.

It is well settled that "[t]he examiner bears the initial burden of factually supporting any *prima facie* case of obviousness. If the examiner does not produce a *prima facie* case, the applicant is under ***no*** obligation to submit evidence of non-obviousness." *Manual of Patent Examining Procedure* (MPEP) § 2142 (8th Ed. Rev. 1, 2003) (emphasis added).

To establish a *prima facie* case of obviousness, the Examiner must show: (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) a reasonable expectation of success; and (3) the prior art reference teaches or suggests all of the claim limitations. MPEP § 2142; *see also In re Vaeck*, 947 F.2d 488. With respect to the motivation to combine the references, the MPEP states "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious

unless ***the prior art also suggests the desirability*** of the combination." MPEP § 2143.01 (emphasis added). If any one of the three elements is missing, a *prima facie* case of obviousness cannot be established.

ii. A summary of the present invention.

Applicants currently claim "[a] method for delivery and retention of an active agent in one or more targeted lymph nodes, comprising: a) injecting into a mammal a first composition comprising ligand conjugated to a colloid; and b) injecting into said mammal a second composition comprising anti-ligand, wherein said anti-ligand binds to said ligand ***prior to entering the lymph node.***" Claim 1 (emphasis added). Applicants also claim "[a] method for detecting one or more sentinel lymph nodes comprising: a) injecting in the vicinity of a tumor in a mammal a first composition comprising ligand conjugated to a colloid; and b) injecting into said mammal a second composition comprising anti-ligand, wherein said anti-ligand binds to said ligand ***prior to entering the lymph node.***" Claim 15 (emphasis added).

As discussed in the following sections, the cited references fail to teach or suggest "wherein said anti-ligand binds to said ligand prior to entering the lymph node." There is also no motivation to combine or modify the cited references to teach such a binding prior to entering the lymph nodes. Additionally, there is no reasonable expectation of success that such a binding prior to entering the lymph nodes would actually work.

iii. The cited references fail to teach or suggest every element of the presently claimed invention.

A necessary element in establishing a *prima facie* case of obviousness requires a showing by the Action that every element of the presently claimed invention is disclosed by the cited references. This has not been done.

The primary reference, Allen *et al.*, appears to be directed towards delivering an anti-tumor compound to a targeted tumor. *See* Allen *et al.*, the Title and Abstract. This reference discloses the parenterally injection of an antibody modified by a ligand molecule to a subject. *Id.* at col. 12, lines 17-26. Subsequently, a liposome having a liposome-entrapped compound, and as surface-bound anti-ligand molecule, are administered perenterally 24 to 48 hours after the injection of the modified antibody. *Id.* The modified antibody is used to bind to a target tumor and then subsequently bind to the liposome/antiligand molecule. *Id.*

By stark contrast, the present invention is directed towards methods "for delivery and retention of an active agent in one or more targeted ***lymph nodes***" or for methods "for detecting one or more ***sentinel lymph nodes***." Allen *et al.* does not appear to even mention lymph nodes—much less delivering an active agent to a targeted lymph node or for detecting a sentinel lymph node.

Allen *et al.* also fails to teach or suggest "wherein said anti-ligand binds to said ligand prior to entering the lymph node." As noted above, the modified antibody in Allen *et al.* is used to bind to a targeted tumor. The liposome/anti-ligand complex subsequently binds to the modified antibody. There does not appear to be any disclosure in Allen *et al.* regarding the subsequent entry of the complex into a targeted lymph node—much less the retention of such a composition in a targeted lymph node.

The secondary references (Griffiths, Gustavson *et al.*, and Oussoren) also appear to be similarly deficient. Griffiths, for example, is directed towards "methods of detecting and/or treating lesions in a patient." Griffiths, Abstract. The method appears to include the parenteral injection of three separate compositions—a targeting composition that binds to a target lesion, a clearing composition that binds to the targeting composition, and a detection or therapeutic

composition that binds to the clearing composition. *Id.* Gustavson *et al.* appears to disclose polymeric carries that include a drug-binding domain. Gustavson *et al.*, Abstract. The polymeric carrier can be attached to an antibody specific for a desired target cell. *Id.* Oussoren appears to concern lymphatic uptake of liposomes after subcutaneous injection. *See* Oussoren, Abstract. The data presented in Oussoren does not appear to be related to the liposomal compositions binding to a second composition prior to entry into the lymphatic system. *Id.*

A commonality of the secondary references is their lack of disclosure relating to "wherein said anti-ligand binds to said ligand prior to entering the lymph node." These references additionally appear to fail to teach the delivery and retention of such a composition into a targeted lymph node or for detecting a sentinel lymph node.

Because the cited references fail to teach or suggest every element of the presently claimed invention, the Action has not shown an essential element of establishing a *prima facie* case of obviousness. The present obviousness rejection, therefore, cannot be maintained.

iv. There is no motivation to combine or modify the cited references.

A second element necessary to establish a *prima facie* case of obviousness requires a showing by the Action that there is a motivation to combine the teachings of the primary reference (Allen *et al.*) with those of the secondary references (Griffiths, Gustavson *et al.*, and Oussoren). This has not been done.

Again, Allen *et al.* appears to be directed towards delivering an anti-tumor compound to a targeted tumor. There does not appear to be any discussion, much less a suggestion, in Allen *et al.* regarding lymph nodes or of delivering an active agent to a targeted lymph node or for detecting a sentinel lymph node. The secondary references similarly fail to contain any discussion, much less a suggestion, "for delivery and retention of an active agent in one or more

targeted lymph nodes" or for methods "for detecting one or more sentinel lymph nodes" where the "anti-ligand binds to said ligand ***prior to*** entering the lymph node." If the Action is basing the combination of the cited references on an "obvious to try" rationale, Applicants note that such a rationale is improper. *See* MPEP § 2145(X). Similarly, reconstruction of Applicants' invention by the use of hindsight is impermissible. *Id.*

Because of the apparent failure of the cited references to disclose any suggestion or motivation to combine or modify their teachings, a necessary element in establishing a *prima facie* case of obviousness has not been established. *See* the MPEP § 2143.01 ("The mere fact that references can be combined or modified does not render the resultant combination obvious unless ***the prior art also suggests the desirability*** of the combination.") (emphasis added). For at least this reason, the present obviousness rejection cannot be maintained.

v. There is no reasonable expectation of success that the combination of the cited references would work.

An additional and independent element necessary to establish a *prima facie* case of obviousness requires a showing of a reasonable expectation of success that combining the teachings of the references would work. This also has not been done by the Action.

Neither the primary or secondary references cited by the Action appear to provide any data suggesting a method for delivery and retention of an active agent or for detecting one or more sentinel lymph nodes "wherein said anti-ligand binds to said ligand prior to entering the lymph node" would work. *See, e.g.*, the cited references. Further, the Action has presented no evidence showing a reasonable expectation of success. Based on the lack of evidence alone, the present obviousness rejection must fall. *See* MPEP § 2142. If the Action is relying on personal knowledge or any reference to support a motivation to combine the teachings of the cited

references, Applicants must request that the Examiner prepare an affidavit and enter it into the file history of this application pursuant to 37 C.F.R. § 1.104(d)(2); *see also* MPEP § 2144.03(C).

In contrast to the lack of evidence presented by the Action and in contrast to the teachings of the cited references, Applicants provide surprising and unexpected data showing the delivery and retention of an active agent to a targeted lymph node or for detecting a sentinel lymph node. *See, e.g.*, the specification, Example 12-19, pages 38-47. Applicants' data is strong evidence that the present invention is ***not*** obvious over the cited references. *See In re Pravin*, 54 F.3d 746, 750 (Fed. Cir. 1995) ("One way for a patent applicant to rebut a prima facie case of obviousness is to make a showing of 'unexpected results,' i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected.").

Because all of the necessary elements required to establish a *prima facie* case of obviousness have not been established by the Action, the present obviousness rejection cannot be maintained.

For at least the reasons stated above, the obviousness rejection for claims 1-19 and 29-30 should be withdrawn.

D. Comments Regarding the Previously Issued Species Election Requirement

The Examiner issued a Species Election Requirement in this case on October 6, 2003. In light of the foregoing remarks, Applicants believe that the present generic claims are allowable. It should be noted, therefore, that upon the allowance of a generic claim, Applicants are entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim. *See* 37 C.F.R. § 1.141(a).

E. Conclusion

Applicants believe that the present document is a full and complete response to the Office Action dated February 17, 2004. It is believed that no fee is due for filing this Response to the Office Action. However, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to this document, consider this paragraph such a request and authorization to withdraw the appropriate fee from Fulbright & Jaworski Deposit Account No. 50-1212/UTSK:343US.

The Examiner is invited to contact the undersigned Attorney at (512) 536-3020 with any questions, comments or suggestions relating to the referenced patent application. Please date stamp and return the enclosed postcard evidencing receipt of these materials.

Respectfully submitted,

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